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VIEWPOINT

A Half Century of Selective Coronary Arteriography

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The first "selective" coronary arteriogram was made 50 years ago by Dr. F. Mason Sones at the Cleveland Clinic. Soon afterward coronary arteriography was developed as a diagnostic method suitable for widespread clinical application. This method has revolutionized our understanding of coronary artery disease and has become the basis for selecting and evaluating therapeutic interventions. This Viewpoint commemorates the achievements of the pioneers of coronary arteriography, the difficulties they encountered, and their impact on the development of modern cardiology. Developments during the last half century and prospects for the future are discussed in historical perspective (J Am Coll Cardiol 2009;54:2139–44) © 2009 by the American College of Cardiology Foundation

The First "Selective" Coronary Arteriogram

On October 30, 1958, at the Cleveland Clinic, Dr. F. Mason Sones studied a 26-year-old man with rheumatic mitral and aortic valve disease. After completing the left ventricular angiogram, he intended to perform an aortogram and placed the closed-end catheter in the ascending aorta, just above the aortic valve. The pressure injector was loaded with 50 ml of contrast material, and Sones climbed down to the pit under the catheterization table, where the huge 11-inch image intensifier was located, to monitor the injection (Fig. 1). He ordered his fellow to fire the pressure injector, but to his astonishment and horror most of the contrast material was delivered directly into the right coronary artery. Fearing the worst, Sones leaped up from the pit and grabbed a scalpel to open the chest and perform open cardiac massage, but to everyone's relief the patient only had asystole for approximately 5 s, followed by sinus bradycardia. After vigorous coughing and an injection of atropine sulfate, normal sinus rhythm was restored, and the patient recovered within a minute, perplexed to see Sones with the scalpel in his hand, ready to attack (1).

The result was the first "selective" coronary arteriogram (Fig. 2). This serendipitous event marked the beginning of a new era in cardiology, in which visualization of the coronary arteries had become possible. In any case, this is how the birth of coronary arteriography is usually remembered, and indeed, how Sones himself liked to describe the historic moment. However, this is only a small part of the complete story, much of which is only remembered by those who were there at the beginning. Today, a half century later, it seems appropriate to commemorate the achievements of the pioneers of coronary arteriography, the difficulties they encountered, and their impact on the development of modern cardiology.

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Earlier Attempts to Visualize the Coronary Arteries

Long before Sones demonstrated the feasibility and safety of intracoronary injections with contrast material, numerous attempts to visualize the coronary arteries had been made. The first attempts in living humans were published in 1945 by Radner (2), who used trans-sternal punctures to inject contrast material into the ascending aorta. Not surprisingly, the complications of this method were too frequent and the results too poor to make it a realistic diagnostic option. Nevertheless, a first step was taken.

A few years later catheterization of the aorta via peripheral arteries was proven to be possible at an acceptable risk for the patients, and interest in visualization of the coronary arteries was rekindled. Special catheters were constructed to deposit contrast material in the coronary sinuses close to the coronary ostia, and additional measures were used to obtain high concentrations of contrast material in the coronary arteries while briefly interrupting or diminishing coronary flow. Some of these methods were quite drastic and not without risk, such as occlusion of the ascending aorta by a balloon catheter and induction of an episode of asystole by injection of acetylcholine (3). Also, Sones experimented with injections of contrast material into the right or left sinuses of Valsalva in dogs in an attempt to opacify their coronary arteries. In some cases these methods, which were later termed semiselective, yielded coronary angiograms of reasonable quality, but the results remained unpredictable and the incidence of complications high.

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Abbreviations and Acronyms

IVUS = intravascular ultrasound

MRI = magnetic resonance imaging

MSCTA = multislice computed tomography angiography

OCT = optical coherence tomography

Today, it may seem surprising that is was several years before selective methods were developed. However, in the late 1950s and early 1960s, X-ray equipment was still primitive, and the available catheters often were more suitable for urological purposes than for arterial catheterization. Furthermore, the risk of intracoronary injections was considered too high, as was voiced by Kolte (4) in 1950: "The danger of introducing an oxygen-free medium into the coronary circulation already seriously compromised by arteriosclerosis is probably great, and anginal pain, dangerous arrhythmias or sudden death are to be feared." Other clinical investigators feared that asymmetrical hypoxia caused by injection of contrast material into one of the coronary arteries could be fatal. These concerns were far from unrealistic, especially because the possibility of dealing with emergency situations was still very limited. It was, for example, not before 1960 that closed-chest massage for cardiac arrest was introduced by Kouwenhoven et al. (5), and endocardial pacing techniques were not yet available.

The Early Development of Selective Coronary Arteriography and What We Learned From the First Visualizations of the Coronary Arteries

Sones immediately recognized the significance of the event of October 1958 and reported the experience to Dr. A. C. Ernstene, head of the Clinic's Department of Cardiovascular Disease. Sones discussed the potential application of selective coronary arteriography by the use of small quantities of contrast material injected manually into the coronary arteries. Ernstene replied: "Go ahead as long as you don't hurt anyone." Soon afterward, Sones and his collaborators were able to demonstrate that the new method of coronary arteriography was safe and, with proper technique, yielded excellent visualization of the coronary arteries in almost all patients. To make cannulation of the coronary arteries possible in an atraumatic manner, Sones designed a catheter that had a relatively thick (8-F, 2.7 mm) and rigid shaft that tapered to a soft and flexible "finger tip" of smaller diameter (5-F, 1.7 mm). In cooperation with the industry, mainly with Philips North America, an X-ray system was developed with a 5-inch image intensifier that was better suited for most patients than the previous larger image intensifier and could be positioned above the patient with the X-ray tube below.

Figure 1 **Sones and the 11-Inch Image Intensifier Used for the First Coronary Arteriogram**

The image intensifier is placed below the catheterization table. The **arrow** points to the 35-mm Arriflex cine camera.

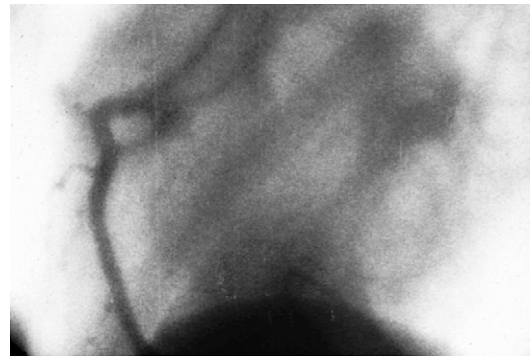

Figure 2 **Right Coronary Artery, Left Anterior Oblique Position**

Frame from the first coronary arteriogram, October 30, 1958.

The news of the results obtained at the Cleveland Clinic spread rapidly throughout the world and attracted hundreds of cardiologists to visit Sones's laboratory, although it was not until 1962 that the first regular publication appeared (6). Many have wondered why the first publication appeared so late. A combination of reasons may account for the delay. Sones first wanted to acquire ample experience with the new method and thought that modifications might be developed that would date the publication, which is probably true in view of the rapid early developments. Furthermore, Sones and his colleague Earl Shirey were under enormous pressure to do catheterizations with limited facilities and personnel, and they could cope only by extending working hours into the evening and night. However, there may have been still another reason. Several (including the authors) who worked with him believed that Sones was dyslexic, which explains his extreme reluctance to write (or read).

The development of a technique of coronary arteriography that was suitable for widespread clinical application is the most spectacular but not the only major contribution of Sones in the field of coronary artery disease. From the beginning he set an example for quality assurance that involved all components of coronary arteriography, ranging from X-ray equipment to film processing. The motivation of Sones and his staff to achieve coronary angiograms of consistently excellent quality was best expressed by Sones and Shirey in the paper (6) they wrote in 1962: ". . . inept performance, inadequate instrumentation, and overimaginative or undiscerning interpretation provide the means of opening a Pandora's box of misinformation which may plague the physician, harm his patients, and retard evolution of a better understanding of human coronary artery disease." The same dedication to reliability is illustrated by an event Dr. Proudfit recalls. Proudfit, a clinical colleague of Sones (in modern terminology a "noninvasive cardiologist"), proposed to do a study on the relation between the clinical history and the findings at coronary arteriography. Sones was much in favor of the idea but insisted that the first thousand patients who had coronary arteriography be excluded and that analysis be confined to the second thousand!

Standardization of arteriographic recordings and reporting often are forgotten but nevertheless essential contributions of the Cleveland Clinic team. At a very early stage Sones and his staff realized that adequate visualization of the coronary arterial tree required that arteriograms be made in multiple projections, which currently may appear obvious but was a new concept at that time. A protocol for optimal visualization of the right and the left coronary artery was developed that was later followed by practically all angiographers, although this involved cumbersome rotations of the patient because rotating gantries had yet to be developed. Furthermore, a semiquantitative system was used to classify obstructions by a visual assessment of the estimated percentage of lumen diameter reduction.

Apart from a new insight into the anatomic changes caused by coronary atherosclerosis, many other phenomena became known in the early days. Coronary artery spasm, that had been suspected to occur, could now be documented; the vasodilative effect of nitroglycerin was proven; myocardial bridging was observed and correctly interpreted; congenital coronary anomalies became much better known; and many other examples can be added. Sones was the first to observe several of these phenomena, but others (7,8) were the first to publish them because he did not.

Sones developed coronary arteriography at a time that many physicians believed that the traditional diagnostic methods were sufficient and the new information was hardly relevant. A typical expression of these thoughts may be found in a leading article (9) about coronary angiography that appeared in *The Lancet* in 1966: "As an aid to diagnosis in ischaemic heart disease it seems at present to offer little that cannot be more easily obtained by much simpler methods such as good history taking and electrocardiography." Apparently the authors did not realize that the reliability of history taking and electrocardiography was assumed rather than proven.

In 1966 Proudfit, Shirey, Sheldon, and Sones (10) published their study on the correlation between clinical findings and coronary arteriography in 1,000 patients and for the first time demonstrated the limitations of history taking. At the same time, their study (10) made it possible to improve the reliability of history taking by showing the sensitivity and specificity of the various characteristics of the patient's complaints. Soon after the clinical findings correlation study was published, coronary arteriography became the standard to which the outcomes of noninvasive diagnostic methods to assess the presence and severity of coronary artery disease were compared. In many cases, this has resulted in improvements of the interpretation and diagnostic value of the noninvasive methods. Although it may sound paradoxical, we may say that the development of noninvasive diagnostic methods to the high accuracy they currently have is based on the availability of coronary arteriography as the gold standard.

At a very early stage Sones and his staff had developed a unique reporting system. From the cine-film, representative frames were selected that were reproduced as enlarged prints on photographic paper. The narrative descriptions of each frame were added in a semistandardized manner. The reports were incorporated in the hospital chart and the laboratory file, and a copy was sent to the referring physician. This reporting system is one of the best, but few laboratories had the facilities and the motivation to follow this cumbersome and time-consuming procedure. Recently this reporting system has regained interest because digital techniques make reproduction of angiographic pictures a great deal easier and allow inclusion of other data in the pictures (e.g., the results of computer-assisted quantitative assessments of obstructions). In addition, the Clinic laboratory files (a huge, and for new investigators somewhat depressingly large, row of books) provided a wealth of information that served as the basis for several original clinical studies on subjects such as the correlation of coronary obstructions with clinical findings and the "natural history" of coronary atherosclerosis (10–12).

Considering Sones's achievements, one can hardly overlook the resemblances between him and the Dutch physiologist and Nobel Prize laureate William Einthoven (Fig. 3). A half century earlier, Einthoven had developed electrocardiography and introduced the standardization of electrocardiogram leads, which is still being used. He also demonstrated the clinical usefulness of his "invention" and interpreted the early electrocardiograms with astonishing accuracy. However, although Einthoven was a quiet and somewhat-introverted person, Sones was quite the opposite!

Early Therapeutic Consequences

From a therapeutic standpoint in the beginning the significance of coronary arteriography was limited and mainly indirect. In patients who were candidates for surgery for congenital or valvular heart disease, information about the coronary anatomy and the presence of coronary atherosclerosis was sometimes useful. Furthermore, demonstration of the absence of coronary atherosclerosis in patients with chest pain could prevent unnecessary medical treatment (at that time mainly consisting of nitroglycerin, sedatives, and anticoagulants) and

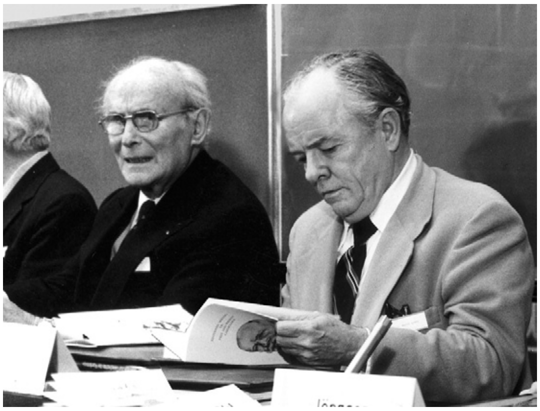

Figure 3 **Sones and Cournand at an "Einthoven Symposium" Held in Leiden, the Netherlands, 1979**

Cournand **(left)** received the Nobel Prize in physiology and medicine together with Forssmann and Richards in 1956 for pioneering work in cardiac and pulmonary physiology and cardiac catheterization. He had been an opponent of left heart catheterization for many years because he thought the risk was too high. Sones **(right)** reads the program of the symposium with Einthoven's portrait. Courtesy of the Einthoven Foundation, Leiden, the Netherlands.

surgical interventions. Various operations for coronary artery disease, such as pericardial poudrage or ligation of the internal thoracic artery (that were supposed to induce the growth of collaterals), and partial occlusion of the coronary sinus were already used long before coronary arteriography became available (13).

Although these efforts were well intended, neither the presence or extent of significant coronary atherosclerosis nor a beneficial effect of surgery could be documented. The real breakthrough came in 1961 when Sones demonstrated angiographically that implantation of the left internal thoracic (then called mammary) artery into the left ventricular wall (method of Vineberg) could provide effective perfusion of the myocardium (14). This was soon followed by other interventions such as endarterectomies and bypass surgery and eventually the percutaneous interventions we know today. Coronary anatomy as defined by coronary arteriography still is one of the cornerstones in the selection of patients for revascularization procedures, together with symptoms, medical therapy, and ischemic burden (15).

Later Developments in Coronary Arteriography

In essence the technique of coronary arteriography has remained the same during the past 50 years, albeit a variety of modifications and extensions have been implemented.

The first extension of coronary arteriography was left ventricular angiography. In the late 1950s, it was the general medical opinion that left ventricular angiography would be dangerous. However, a combined procedure was performed in August 1960 and went well. Later left ventriculograms were performed in patients with clinical findings of a heart murmur, cardiomegaly, or possibly a ventricular aneurysm. Eventually left ventricular angiography became routine in all patients.

A major modification was introduced by Dr. Melvin P. Judkins, who described his percutaneous transfemoral approach (Seldinger technique) in 1967; Sones had always used a brachial arteriotomy to insert the catheter. To facilitate cannulation of the coronary ostia, Judkins used pre-bent "coronary-seeking" catheters. In the beginning Judkins used full-size serial cut film for the arteriographic recordings (16). This technique yielded excellent pictures but soon proved to be too cumbersome and therefore added to the risk of the procedure. Subsequently Judkins followed Sones's example of recording on 35-mm cine-film.

For some years the community of coronary angiographers was divided between strong proponents of the "Sones technique" and equally strong proponents of the "Judkins technique." Contrary to what one might suspect, Sones and Judkins did not regard each other as rivals but each held the other in high esteem. They also shared a dislike for colleagues who had little experience but philosophized freely about the outcomes and presumed shortcomings and virtues of coronary arteriography. They were both founding fathers of the Society for Cardiac Angiography (now renamed the Society for Cardiac Angiography and Interventions); typically, they insisted that to qualify for Fellowship in the Society the candidate should have extensive experience in catheterization and angiography and should have performed personally at least 1,000 coronary arteriographies. Initially the Judkins technique was plagued by complications related to the sharp edge of the end-hole that could cause coronary dissections, but improvements in catheter design have enhanced the safety of this method to the same level as the Sones technique. Currently most angiographers prefer the transfemoral approach, but the transradial approach and, to a lesser extent, the transulnar approach are increasingly used.

In the meantime the cumbersome rotations of the patient were facilitated by a rotating "cradle," which may now seem a minor detail but was of great practical significance then. Subsequently gantries with rotating U-arms became available. This also made the use of caudal-cranial angulations in addition to the conventional left and right anterior oblique projections possible as was first reported by Ludwig and Bruschke (17) in 1973.

The image intensifiers, initially equipped with a mirror that allowed only one person to observe the catheter maneuvers and contrast injections, were later connected with video chains and play-back equipment, which greatly facilitated the training of angiographers. Sophisticated computer-assisted systems, which are still continuously being improved, were developed to accurately and objectively analyze atherosclerotic lesions. These techniques, often termed quantitative coronary arteriography, are helpful in clinical decision making and indispensible in clinical research projects using coronary arteriographic data (18).

Digital recordings have almost completely replaced photographic cine recordings, and an increasing number of image intensifiers are being replaced with solid-state flat-panel systems. Improvements of the physical properties of catheters by the use of modern materials and production techniques and the development of nonionic low- and iso-osmolar contrast media have significantly contributed to the safety of the procedures.

Looking back at the many improvements that have been implemented during the last half century, it is difficult to imagine how this new diagnostic modality could flourish and provide a basis for interventions when, compared with the current situation, the technical facilities were still very primitive. Part of the explanation is that many clinicians and clinical investigators, despite the widespread but decreasing skepticism, realized that coronary arteriography would dramatically improve our understanding of coronary artery disease and open immense possibilities for interventions.

It is an intriguing question whether coronary arteriography would have developed to its current perfection if it hadn't been for Sones's perseverance and the dedication of his team or if, for instance, the first patient had died. Considering the essential contributions of many others who have been committed to the development of coronary arteriography, we believe that the answer should be: yes, but many years later and too late for thousands of patients who now could be diagnosed and treated effectively.

Limitations of Coronary Arteriography and the Merits of Complementary Invasive Investigations

Like any other diagnostic method, coronary arteriography has inherent limitations. It demonstrates the coronary arterial lumen but provides no direct information about changes of the vessel wall. Furthermore, it may be impossible to accurately depict lesions with very complex morphology, and identification of vulnerable plaques is rarely possible (19). These shortcomings can be minimized but not conquered by optimal angiographic technique, expert interpretation, and state-of-the-art computer-assisted quantitative analysis (18). A variety of intravascular imaging techniques have been developed to compensate for the limitations of coronary arteriography (20). Catheter-based techniques that use intravascular ultrasound (IVUS) have been used for many years and have provided new insights into vascular biology. In practice IVUS is currently widely used to guide percutaneous interventions. Optical coherence tomography (OCT) is an emerging technique that is based on the same principles as IVUS but uses near-infrared light, which provides for a much greater resolution than is achievable with ultrasound. However, OCT has less penetrability through nontransparent tissue and image acquisition is hampered by the presence of blood (21). The greater resolution should make OCT more suitable than IVUS to identify unstable plaques, but noninvasive imaging techniques such as molecular imaging using ^{18}F-FDG positron emission tomography or annexin imaging with single-photon emission computed tomography may prove to be more accurate and practical for this purpose (22).

Without detracting from the merits of newer intravascular imaging modalities, we must realize that a complete analysis of the coronary anatomy should include coronary arteriography. The arteriogram depicts the anatomy of the entire coronary artery tree, it demonstrates collateral channels, and provides information about small vessels and vessel segments distal to severe obstructions or occlusions that are inaccessible to other intravascular techniques. Furthermore, even if an exact 3-dimensional reconstruction of the vascular lumen is possible by IVUS or OCT, it may still be impossible to determine the functional significance of complex obstructions solely on the basis of morphologic characteristics. For hemodynamic evaluations physiologic tests such as assessment of fractional flow reserve, which represents the ratio of maximal flow in a stenotic artery to the normal maximal flow and may be derived from intracoronary pressure measurements, are more appropriate (23). In summary, new intravascular techniques have significantly contributed to the value of invasive investigations and have become an essential part of the diagnostic armamentarium; however, they cannot replace the "traditional" coronary arteriography.

Will Coronary Arteriography Eventually Become Obsolete?

Although coronary arteriography is a relatively safe procedure, it still is an invasive technique with risks that cannot be completely avoided. During the past decade, 2 techniques for noninvasive coronary arteriography have emerged, that is, magnetic resonance imaging (MRI) and multislice computed tomography angiography (MSCTA). At present the accuracy of MSCTA in defining coronary anatomy is considerably greater than that of MRI, and therefore MSCTA is the most realistic option for noninvasive imaging of the coronary arteries (24). Like coronary arteriography, MSCTA is an angiographic technique, but it requires no catheterization (and is therefore free of catheterization-related complications) and provides true 3-dimensional images. The negative predictive value of MSCTA is very high, which makes the method particularly suitable to rule out coronary atherosclerosis in patients with a low or intermediate pre-test likelihood of disease (25).

However, in "positive" cases MSCTA overestimates the severity of atherosclerotic lesions, and at this stage MSCTA cannot be used as a substitute for coronary arteriography in patients with significant obstructive coronary artery disease (26). The technologies of MRI and MSCTA are still improving, and the future will tell us if eventually these or other noninvasive diagnostic methods can entirely replace coronary arteriography. Should this be the case, then we may not forget that the development and validation of new techniques to depict coronary anatomy are based on the work of Dr. F. Mason Sones and numerous other dedicated pioneers like Dr. Melvin P. Judkins.

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